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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,175	GLORIOSO ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *5-11,13,14,16,18,24,27-44 and 46-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 12, 15, 17, 19-23, 25, 26 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Response filed 7-1-03 has been received and entered.

2. Claims 1-48 are pending.

3. Applicant's election of the invention of group V, claims 1, 2, 12, 15, 17, 19, 20, 22, 23, 25, 26 and 45 is acknowledged.

4. Applicant's election with traverse of group V, claims 1, 2, 12, 15, 17, 19, 20, 22, 23, 25, 26 and 45 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that claims must be examined if there is not undue burden and that undue burden has to be established. This is not found persuasive because as discussed in the previous office action of 5-30-03, it was discussed as to how inventions of different groups would have required separate and non-coextensive searches in the patent and non-patent literature.

The requirement is still deemed proper and is therefore made FINAL.

5. Applicants requested to include claims 3, 4 and 21 in group V and in view of compact prosecution and customer service, the claims have been added to group V. Accordingly, claims 1-4, 12, 15, 17, 19-23, 25, 26 and 45 (drawn to an ex vivo method of gene therapy using IL-1 receptor) now constitute group V. and are therefore under consideration.

6. Claims 5-11, 13, 14, 16, 18, 24, 27-44 and 46-48 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10 and 12.

7. Claims 1-4, 12, 15, 17, 19-23, 25, 26 and 45 (drawn to an ex vivo method of gene therapy using IL-1 receptor) are under consideration.

8. Claims 1 is objected to because it recites non-elected invention. Applicants are required to amend claim 1 to reflect elected invention.

9. It is noted that the application claims priority to several US non-provisional applications as being CIP of these applications. Sometimes an application in the priority list is a CIP of two applications. It is therefor difficult to determine at what time a particular change to the specification was made. Therefore, instant

application is assigned a priority date of September 5, 1997, the priority date of the parent 08/924, 777.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-4, 12, 15, 17, 19-23, 25, 26 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a arthritis in a mammalian host, generating a recombinant viral vector comprising a DNA sequence encoding soluble IL-1 receptor operatively linked to a promoter, infecting in vitro a population of autologous cultured synovial cells with said recombinant viral vector resulting in a population of transduced synovial cells and transplanting said transduced synovial cells by intraarticular injection to an arthritic joint space of a mammalian host, such that expression of said DNA sequence in said joint space results in a reduction of cartilage destruction or a reduction in synovitis, does not reasonably provide enablement for any other limitation encompassed by the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As instantly presented claimed invention encompasses treatment of any connective disorder in a mammal host by transplanting any cell at any site in the host wherein the cell is transduced with any vector that comprises a DNA that expresses any IL-1 receptor or a fragment thereof. However, the specification as filed does not provide any guidance as to how an artisan of skill would have practiced the claimed method commensurate with the full scope of the claims

because the art of gene therapy by transplanting any cell expressing any IL-1 receptor or fragment is unpredictable and therefore would require undue experimentation for an artisan of skill to practice the claimed invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification as filed teaches cDNA encoding the IRAP, direct intraarticular injection of IRAP viral vector to the knee of a rabbit, transfection of synoviocytes with the viral vector, retroviral vector expressing a soluble IL-1 receptor, anti-inflammatory properties of IRAP transgene expression (see the figures and the examples). The specification does not provide any working examples for treating a connective disease by transplanting cells expressing IL-1 receptor. The specification is not enabling for the claimed invention commensurate with the full scope of the claims because the art of ex vivo gene therapy for any connective tissue disease was not predictable for reasons discussed below and therefore an artisan of skill would have required undue experimentation to practice the claimed invention.

First, can delivery of a cell expressing any IL-1 receptor treat any connective tissue disease? While the relationship of increased IL-1 to causes arthritis and treatment of arthritis by administering IL-1 receptor antagonist is known (Bandara et al. Proc. Natl. Acad. Sci. USA. Vol 90:10764-10768, 1993), the specification does not teach as to how administration of full length IL-1 receptor will treat arthritis or any condition since it will interact with IL-1 and produce signal transduction that are responsible for the pathological condition. One would rather expect enhancement of the disease condition. Regarding, the issue of any fragment of IL-1 receptor, while the specification teaches a soluble form of the receptor, the specification does not teach what parts of the receptor could be removed and the resultant could still bind to IL-1 and treat the connective tissue disease. Next, the specification does not teach how to target the expression of IL-1 receptor to arthritis joints by transplanting cells to a host at any site. Bandara et al (Bandara et al. DNA and Cell Biology 11 :227-231, 1993) noted that joints are difficult organs to target therapeutically and the therapeutic agent administered by intravenous, intramuscular or oral routes systemically affects the entire body and therefore drug is not optimally available to the site of treatment. The specification does not provide any guidance as to how the cells transplanted at any site will be able to provide the IL-1 receptor to arthritis affected joints or to connective tissue disease site. It is noted that the cells have to express the IL-1 receptor, which has to be reach the disease site. Next, as instantly presented, claimed invention encompasses xenogeneic and allogeneic cell transplantation, however the specification does not teach as to how transplant cell of xenogeneic or allogeneic source which will elicit immune response that will further increase the immune reaction at the connective disease site. It is noted that use of cells in therapy require several consideration of source of cells, type of tissue damage to be repaired by cell transplantation etc (see Hammer C. Blood Purification 19:322-328, 2001). The specification does not teach as to how would an artisan have used any cell of any source in the transplantation for treating any connective disease.

In view of the discussion above, an artisan of skill would have required undue experimentation to practice the claimed invention commensurate with the full scope

of the claims and therefore limiting the scope of the claimed invention to a method of treating a arthritis in a mammalian host, generating a recombinant viral vector comprising a DNA sequence encoding soluble IL-1 receptor operatively linked to a promoter, infecting in vitro a population of autologous cultured synovial cells with said recombinant viral vector resulting in a population of transduced synovial cells and transplanting said transduced synovial cells by intraarticular injection to an arthritic joint space of a mammalian host, such that expression of said DNA sequence in said joint space results in a reduction of cartilage destruction or a reduction in synovitis is proper.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-4, 12, 15, 17, 19-23, 25, 26 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites the step "transducing a population of target cells" however, it is unclear whether the transduction is in vivo or in vitro. The specification does not describe whether the transduction is in vitro or in vivo and therefore the metes and bounds of the claimed invention are not unclear.

Claims 22 and 23 are indefinite because they recite abbreviated forms of words, such as MFG vector, sIl-1r type etc. Using the full form of the terms with the abbreviated form in parenthesis when recited first time will obviate the rejection.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 1-4, 12, 15, 17, 19-23, 25, 26 and are 45 rejected under 35 U.S.C. 103(a) as being unpatentable over and Dower et al (US 5,492,888, 2-20-1996, effective filing date November 25, 1987) in view of Bandara et al (Bandara et al. DNA and Cell Biology 11 :227-231, 1993).

Dower et al teaches methods of using soluble human IL-1 receptors for suppressing immune responses (see the claims). The patent teaches expression vector for expressing soluble IL-1 receptor and method of culturing and transfecting cells with the expression vector (see columns 4, 5, 20-24 and example 1-3). The patent also teaches suppression of inflammatory arthritis by local administration of soluble IL-1R in rats (see example C-E and 5). Dower et al does not teach transplantation of IL-1 receptor expressing cells to a mammalian host for treating a connective tissue disease.

Bandara et al teaches gene transfer to synoviocytes as a method for treating arthritis by gene therapy (see the entire article). This art discusses the merits of gene delivery to synovium for treating arthritis. The art also teaches removal of synovium from a joint of a mammal, transduction of the cells in vitro and reintroduction of the transduced cells into the joint (see figure 1). The at further teaches that synovial cells infected with retroviral vector expressing LacZ when injected in the knee joint of a rabbit showed the expression of Lac Z (see the right

column on page 229 continued in the left column on page 230). The art further discusses that the gene transfer system provides an opportunity to deliver gene whose products antagonize the action of IL-1.

At the time of the invention, it would have been obvious to an artisan of ordinary skill to transfect the synovial cells of Bandara et al with the expression vector of Dower et al or modify the retroviral vector of Bandara et al by cloning the DNA encoding the soluble IL-1 receptor and transfect the synovial cells and inject them in the joints of a mammal with a reasonable expectation of success. An artisan would have been motivated to make such expression vectors or transfected cells and transplanted them in joints because soluble IL-1 receptor expression in the joints would have inhibited the immune response in the arthritis joints and treated the arthritis.

16. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. The after-final fax number is (703) 87209307. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

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Primary Examiner
Art Unit 1632